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 NEWS  3   Feb  1  Addition of Machine-Translated Abstracts to CAplus
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 NEWS  9   Feb 28  Patent Information Now Searchable in CAOLD
 NEWS 10   Mar  1  New IMSDIRECTORY Provides Pharma Company Details
 NEWS 11   Mar 20  INPADOC: PRODUCER WARNING ABOUT DATA DELAYS
 NEWS 12   Mar 22  NEW FEATURES IN INPADOC - RANGE SEARCHING AND NEW
                   SDI/UPDATE SEARCH FIELD

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=> file morphine?/cn

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specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> s morphine?/cn

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=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

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DICTIONARY FILE UPDATES: 12 APR 2000 HIGHEST RN 261737-57-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 11, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> s morphine?/cn

L1 353 MORPHINE?/CN

=> file medline, uspatfull, hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.90	4.05

FILE 'MEDLINE' ENTERED AT 14:40:39 ON 13 APR 2000

FILE 'USPATFULL' ENTERED AT 14:40:39 ON 13 APR 2000
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=> s l1

L2 41020 L1

=> s ph

L3 2419314 PH

=> s l2 and l3

L4 5235 L2 AND L3

=> s (sulfate# or sulphate#)

L5 657070 (SULFATE# OR SULPHATE#)

=> s l4 and l5

```
L6          573 L4 AND L5

=> file reg

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        17.36      21.41

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STRUCTURE FILE UPDATES:   12 APR 2000  HIGHEST RN 261737-57-9
DICTIONARY FILE UPDATES:  12 APR 2000  HIGHEST RN 261737-57-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 11, 2000

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> s morphine sulfate/cn

L7            1 MORPHINE SULFATE/CN

=> s l7 and ph

          2973 PH
L8             0 L7 AND PH

=> file medline, uspatfull, hcaplus

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         7.80      29.21

FILE 'MEDLINE' ENTERED AT 14:43:50 ON 13 APR 2000

FILE 'USPATFULL' ENTERED AT 14:43:50 ON 13 APR 2000
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=> s l7 and ph

L9           117 L7 AND PH

=> s nasal? or intranasal? or nose#

L10       141912 NASAL? OR INTRANASAL? OR NOSE#

=> s l9 and l10

L11           10 L9 AND L10

=> dup rem l11

PROCESSING COMPLETED FOR L11
L12           10 DUP REM L11 (0 DUPLICATES REMOVED)
```

=> d bib,ab,kwic l12 1-10

L12 ANSWER 1 OF 10 USPATFULL
AN 1999:110488 USPATFULL
TI Therapeutic compound-fatty acid conjugates
IN Whittaker, Robert George, West Pymble, Australia
Bender, Veronika Judith, Cremorne, Australia
Reilly, Wayne Gerrard, Northmead, Australia
Moghaddam, Minoo, Killara, Australia
PA Commonwealth Scientific and Industrial Research Organisation, Campbell, Australia (non-U.S. corporation)
PI US 5952499 19990914
WO 9622303 19960725
AI US 1997-875098 19970925 (8)
WO 1996-AU15 19960115
19970925 PCT 371 date
19970925 PCT 102(e) date
PRAI AU 1995-580 19950116
AU 1995-581 19950116
AU 1995-582 19950116
AU 1995-583 19950116
AU 1995-584 19950116
AU 1995-585 19950116
AU 1995-586 19950116
DT Utility
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Badio, Barbara
LREP McDermott, Will & Emery
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A methotrexate conjugated to 1-3 acyl groups derived from fatty acids. In particular the invention relates to altering the pharmacokinetic profile and mode of delivery of methotrexate by conjugating it to 1.2 or
3 acyl derivatives of fatty acids.
SUMM . . . over the unconjugated therapeutic agent. Further it is believed
that these novel compounds will aid in the oral, transdermal, intraarticular, **intranasal**, and/or intraocular delivery of these drugs.
SUMM . . . by any appropriate route as will be recognised by those skilled
in the art. Such routes include transdermal, intraarticular, oral, **intranasal** and intraocular.
SUMM . . . that such new compounds will improve the delivery, uptake, half-life and targeting within the cell of the drug after oral, **intranasal**, transdermal, intraocular and other modes of delivery. Further it may change the distribution of the drug in the body
increasing. . .
SUMM . . . be administered by any appropriate route as will be recognised by those skilled in the art. Such routes include oral, **intranasal**, transdermal and intraocular.
SUMM . . . of the cyclosporin family of drugs. Further it is believed that
these novel compounds will aid in the oral, transdermal, **intranasal**, parenteral and/or intraocular delivery of these drugs by facilitating their transport across lipophilic membranes.
SUMM . . . administered by any appropriate route as will be recognised by those skilled in the art. Such routes include oral, transdermal, **intranasal**, parenteral and intraocular.

SUMM . . . distribution into the CNS of these drugs. Further it is believed that these novel compounds will aid in their oral, **intranasal**, transdermal, intratumoural, parenteral, intraarticular and/or intraocular delivery.

SUMM . . . be administered by any appropriate route as will be recognised by those skilled in the art. Such routes include oral, **intranasal**, transdermal, intratumoural, parenteral, intraarticular and intraocular.

SUMM . . . blood-brain barrier and improve its half-life. Further it is believed that these novel compounds will aid in the oral, transdermal, **intranasal**, parenteral and/or intraocular delivery of this drug. ##STR18##

SUMM . . . administered by any appropriate route as will be recognised by those skilled in the art. Such routes include oral, transdermal, **intranasal**, parenteral and intraocular.

SUMM . . . and/or mode of delivery of the drugs. Further it is believed that these novel compounds will aid in their oral, **intranasal**, transdermal, parenteral, intratumoural and/or intraocular delivery. ##STR21##

SUMM . . . be administered by any appropriate route as will be recognised by those skilled in the art. Such routes include oral, **intranasal**, transdermal, parenteral, intratumoural and intraocular.

DETD . . . The solvent was removed under vacuum and the residue redissolved in DCM and washed with water several times until the **pH** equalled 7. The organic phase was dried (MgSO.sub.4) and evaporated to afford a light yellow solid. The crude product was. . .

DETD . . . was partitioned between DCM (50 ml) and H.sub.2 O (50 ml), TEA was added to the aqueous phase until the **pH** was >7. Upon this time acetic acid was added until the **pH** reached 3-4. The organic phase was collected and washed with H.sub.2 O (50 ml). dried (Na.sub.2 SO.sub.4) and solvent removed.. . .

DETD . . . to a stirred solution of Z.sub.3 -DOPA (1.68 g, 2.8 mmol) in acetonitrile (20 ml) and DIEA (550 ul to **pH** 8.50). The reaction was followed by HPLC and monitored at 300 nm. After 10 min the reaction was complete and. . .

DETD . . . was reacted with a solution of TPTU (1 g, 3.4 mmol) in acetonitrile (5 ml) and DIEA (350 ul, to **pH** 8.3) and the formation of active ester monitored by HPLC in System II at 300 nm. The reaction was complete. . .

DETD . . . precipitate was filtered and the filtrate washed with 5% acetic acid aqueous solution, then H.sub.2 O three times until the **pH** was 7. The organic phase was dried (MgSO.sub.4), then concentrated in vacuo. The crude product was purified by the flash. . .

IT 50-23-7, Hydrocortisone 57-10-3, Hexadecanoic acid, reactions 59-92-7, L-Dopa, reactions **64-31-3**, Morphine sulfate 108-30-5, Succinic anhydride, reactions 305-03-3, Chlorambucil 501-53-1, Benzyl chloroformate 6066-82-6, N-Hydroxysuccinimide 30516-87-1, AZT 74124-79-1, N,N'-Disuccinimidyl carbonate 91202-74-3 116907-82-5, 17-Epihydrocortisone 167986-15-4 167986-16-5 167986-17-6
(prepn. of fatty acid conjugates and their pharmacol. activity)

L12 ANSWER 2 OF 10 USPATFULL

AN 1999:99399 USPATFULL

TI Pharmaceutical compositions for **intranasal** administration of dihydroergotamine

IN Merkus, Franciscus W. H. M., Grootreesdijk 26, Kasterlee, Belgium

PI US 5942251 19990824

AI US 1998-62633 19980417 (9)

RLI Division of Ser. No. US 525771

PRAI BE 1993-297 19930326
BE 1993-298 19930326
BE 1993-299 19930326

DT Utility
EXNAM Primary Examiner: Reamer, James H.
LREP Jones, Day, Reavis & Pogue
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 602
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to pharmaceutical compositions for the **intranasal** administration of dihydroergotamine, apomorphine and morphine comprising one these pharmacologically active ingredients in combination with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.
TI Pharmaceutical compositions for **intranasal** administration of dihydroergotamine
AB The invention relates to pharmaceutical compositions for the **intranasal** administration of dihydroergotamine, apomorphine and morphine comprising one these pharmacologically active ingredients in combination with a cyclodextrin and/or a disaccharide. . .
SUMM This invention is related to pharmaceutical compositions for **nasal** administration of dihydroergotamine, apomorphine and morphine, and methods of administering such compositions.
SUMM . . . for oral application, as well as for acute treatment by intravenous or intramuscular injection. DHE has been introduced in a **nasal** spray to avoid the parenteral and the oral route of administration. The **nasal** spray seems a good alternative, because it is less painful, less expensive and less inconvenient than injection therapy. Secondly, nausea and vomiting are common in migraine patients, making a **nasal** spray much more efficient than oral treatment.
SUMM A **nasal** spray containing DHE 4 mg/ml in an aqueous solution has been studied extensively by a number of investigators. Some of these investigators report, that besides DHE the **nasal** spray also contains glucose 5% and caffeine 1%. It was found that 1 mg of DHE, **nasally** administered, had the equivalence of 10 mg orally, and almost 40% of the bioavailability of the i.m. administration (P G. . .
SUMM The maximal venoconstrictor effect of 1 mg **nasal** DHE amounted to about 40%, of 0.5 mg i.m. DHE to about 50% of the initial venous diameter (W. H.. . .
SUMM **Nasal** DHE appeared to be equally effective than a combination of oral ergotamine and caffeine in relieving migraine attacks (D. Hirt et al, Cephalalgia 1989; 9, suppl. 10: 410-411). Another study in 904 patients confirmed the efficacy of **nasal** DHE and reported side effects in 18.4% of patients: **nasal** irritation, nausea, vomiting, fatigue, vertigo, breathlessness, tachycardia and perspiration. Only 3.9% of the patients refused further treatment with **nasal** DHE (G. Jenzer and M. F. Bremgartner, Schweiz. Rundsch. Med. Prax. 1990: 79: 914-917). Lataste et al (Cephalalgia 1989; 9 suppl. 10: 342-343) and Di Serio et al (Cephalalgia 1989; 9 suppl. 10: 344-345), confirm the efficacy of **nasal** DHE in the acute management of migraine. In contrast, Tulunay et al (Cephalalgia 1987; 7: 131-133) found little difference in **nasal** DHE and placebo.
SUMM Most of these studies are very encouraging and therefore **nasal** DHE, in the pharmaceutical composition studied by the above mentioned authors, seems an interesting alternative for oral and parenteral DHE preparations. **Nasal** DHE in the composition of DHE mesylate 4 mg/ml in 5% glucose and 1% caffeine, is available on prescription in. . .
SUMM Nevertheless, there is an urgent need for another DHE **nasal** drug formulation, because the **nasal** preparation, presently on

the market, is not stable. It is on the market as a separate glass ampoule (containing the DHE formulation) which has to be broken by the patient and sprayed in the **nose** using a separate spray device. After opening of the ampoule, the spray can be used no longer than 24 hours.

SUMM Accordingly, it is an object of the invention to provide a highly stable pharmaceutical composition, suitable for **nasal** administration, capable of introducing efficiently a therapeutical amount of DHE into the human body. It has surprisingly been found that a pharmaceutically acceptable DHE composition can be formulated, suitable for **nasal** administration, without the presence of a special caffeine-glucose vehicle and without the necessity of presenting the formulation in a separate. . .

SUMM According to the invention, the **nasal** pharmaceutical composition contains DHE and/or a salt of DHE (mesylate or tartrate) and a cyclodextrin and/or other saccharides and/or sugar. . .

SUMM The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

SUMM . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

SUMM **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

SUMM . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

SUMM The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of DHE in the **nasal** pharmaceutical composition of the invention, suitable in the treatment of migraine attacks, are preferably in the range from 0.25 to. . .

DETD . . . adjunctive medication in the treatment of Parkinson's disease, complicated by motor fluctuations. Recently, encouraging results have been reported on the **intranasal** application of apomorphine in patients with Parkinson's disease to relieve "off-period" symptoms in patients with response fluctuations (T. van Laar et al, Arch. Neurol. 1992; 49: 482-484). The **intranasal** applied apomorphine, used by these authors, consisted of an aqueous solution of apomorphine HCl 10 mg/ml. This formulation is also. . .

DETD The exact **nasal** composition formulation used in the study by T. van Laar et al (1992) was:

DETD . . . g

Sodium EDTA	0.010	g
NaCl	0.600	g
Benzalkonium Chloride	0.01%	
NaH.sub.2 PO.sub.4.2H.sub.2 O	0.150	g
Na.sub.2 HPO.sub.4.2H.sub.2 O	0.050	g
NaOH 1 M to adjust **pH** at	5.8	

purified water to 100 ml
(from Pharm. Weekblad 1991; 126: 1113-1114)

DETD . . . a metered dose nebulizer a dose of 1 mg apomorphine HCl (0.1 ml of the solution) was delivered with each **nasal** application by puff to the patients. A great disadvantage of this aqueous solution is the instability of the apomorphine.

DETD . . . water soluble alkaline stabilizer. The compositions described in EP A 475 482 are not appropriate and of no significance for **nasal** apomorphine administration.

DETD . . . of drugs such as polypeptides, polysaccharides, aminoglycosides, .beta.-lactam antibiotics and nucleic acids in combination with a cyclodextrin, preferably .alpha.-cyclodextrin, for **nasal**, vaginal or rectal administration. The drug apomorphine does not belong to any of the drug groups mentioned by EP 0. . .

DETD EP A 463 653 discloses **intranasal** pharmaceutical compositions, in which cyclodextrins are added to a **nasal** drug formulation to reduce the undesirable side effect of the absorption enhancer in the formulation such as chelating agents, fatty acids, bile acids salts, surfactants, fusidic acid, lysophosphatides and cyclic peptide antibiotics. The main purpose is to protect the **nasal** mucosa from the undesirable effects of these absorption enhancers by adding a cyclodextrin to the formulation (col. 8, line 40-42).. . . reduce the toxic effects of absorption enhancers including Laureth-9, Deoxycholic acid Sodium and L-.alpha.-lysophosphatidylcholine Palmitoyl. For the preparation of a **nasal** apomorphine composition according to the present invention, no such absorption enhancers are present or needed.

DETD An object of the invention is a **nasal** formulation of apomorphine with an improved bioavailability and stability of apomorphine.

DETD According to the invention, the **nasal** pharmaceutical composition contains apomorphine and/or apomorchine salts and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such compositions appear to. . .

DETD The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

DETD . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

DETD **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

DETD . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

DETD The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of apomorphine in. . .

DETD

Apomorphine HCl	500	mg
Methylated-.beta.-cyclodextrin	D.S. 1.8	
Hydroxypropylmethylcellulose	2.5	g

	1-2	g
Benzalkonium Chloride	0.01%	
Sodium EDTA	0.1%	
Sodium metabisulphite	0.15%	
Sorbitol	4%	
pH adjusted to	4.5-5.5	
purified water to	100	ml

0.2 ml gel = 1 mg Apomorphine HCl

DETD . . . when the parenteral route is impractical or undesirable and the oral route is not available due to the patients condition. **Nasal** administration of a strong analgesic could be a good alternative to parenteral therapy, because it may give a very rapid. . .

DETD To overcome the drawbacks of the oral and parenteral routes of administration of morphine, the use of a **nasal** spray has been proposed (S. L. Verweij and R. van Gijn: Can morphine be administered **nasally**? Ziekenhuisfarmacie (Dutch) 1988; 4: 73-77). The composition of the **nasal** spray in this study was:

DETD

Morphine HCl.3H.sub.2 O	1.50	g
Sodium metabisulphite	0.03	g
Sodium EDTA	0.003	g
Benzylalcohol	0.3	ml
Propylene glycol	6	ml
Phosphate Buffer (0.01 mol/L; **pH** 6.00)	30	ml

Per puff of 100 .mu.l the dose of morphine is 5 mg.

DETD . . . was delivered to the volunteers was 16 mg of morphine (range 15-18 mg) and the bioavailability of morphine from this **nasal** spray was 26-35%. The bioavailabilty of morphine after oral application is estimated to be about 40% (J. Sawe, Clin. Pharmacokinetics 1986; 11: 87-106). This means, that the bioavailability of morphine after giving the **nasal** spray as described by Verweij and van Gijn is relatively low. After **nasal** absorption there is no first pass effect and therefore the **nasal** bioavailability should be higher than the oral.

DETD The **nasal** absorption of morphine has been studied also by F Chast et al (J. Pharm. Clin. 1992; 11: 257-261). They delivered **nasally** and orally 20 mg morphine acetate in an aqueous solution to 6 patients and compared the **nasal** absorption with the oral absorption of the same solution. They found, as expected, higher blood levels of morphine after the **nasal** application. Unfortunately, the **nasal** solutions, as described by the preceding studies of Verweij and van Gijn and of Chast and coworkers, are not stable. . .

DETD An object of the invention is to provide a highly stable pharmaceutical composition, suitable for **nasal** administration, and showing an superior bioavailability of morphine.

DETD According to the invention, the **nasal** pharmaceutical composition contains morphine and/or morphine salts (hydrochloride, sulphate, acetate) and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such. . .

DETD The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

DETD . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in

chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

DETD **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

DETD . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

DETD The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril.

CLM What is claimed is:

1. A pharmaceutical composition for **nasal** administration of a pharmacologically active ingredient to be absorbed through the **nasal** mucosa, wherein the pharmacologically active ingredient is selected from the group consisting of dihydroergotamine, dihydroergotamine salts and mixtures thereof, and. . .

8. A process for preparing a **nasal** pharmaceutical composition comprising combining a pharmaceutically active ingredient selected from the group consisting of dihydroergotamine, dihydroergotamine salts and mixtures thereof. . .

9. A method of treating migraine attacks comprising administering to the **nasal** mucosa of a patient a pharmaceutical composition comprising a pharmacologically active ingredient selected from the group consisting of dihydroergotamine, dihydroergotamine. . .

14. A pharmaceutical composition for **nasal** administration consisting essentially of (a) a pharmacological active ingredient for absorption through the **nasal** mucosa and selected from the group consisting of dihydroergotamine, dihydroergotamine salts and mixtures thereof, (b) an ingredient selected from the. . .

25. A pharmaceutical composition for **nasal** administration, consisting essentially of (a) a pharmacological active ingredient for absorption through the **nasal** mucosa and selected from the group consisting of dihydroergotamine, dihydroergotamine salts and mixtures thereof, and (b) an ingredient selected from. . .

IT 50-70-4, D-Sorbitol, biological studies 52-26-6, Morphine hydrochloride 58-00-4, Apomorphine 63-42-3, Lactose **64-31-3**, Morphine sulfate 69-65-8, D-Mannitol 314-19-2, Apomorphine hydrochloride 511-12-6, Dihydroergotamine 596-15-6, Morphine acetate 5989-77-5, Dihydroergotamine tartrate 6190-39-2, Dihydroergotamine mesylate 7585-39-9, .beta.-Cyclodextrin 7585-39-9D, .beta.-Cyclodextrin, Me ethers 9004-54-0, Dextran, biological studies 10016-20-3, .alpha.-Cyclodextrin 17465-86-0, .gamma.-Cyclodextrin (intranasal compns. contg. therapeutic agents and cyclodextrins and saccharides)

L12 ANSWER 3 OF 10 USPATFULL

AN 1999:63321 USPATFULL

TI Synergistic composition of codine and ibuprofen to treat arthritis

IN Miller, Ronald Brown, Basel, Switzerland
Douglas, Stephen Gordon, Shropshire, United Kingdom
Miller, Allan John, Surrey, United Kingdom

PA Euro-Celtique, S.A., Luxembourg, Luxembourg (non-U.S. corporation)

PI US 5908848 19990601

AI US 1997-855848 19970512 (8)

RLI Continuation of Ser. No. US 1996-584658, filed on 11 Jan 1996, now patented, Pat. No. US 5763452 which is a continuation of Ser. No. US

1994-310640, filed on 22 Sep 1994, now abandoned
PRAI GB 1993-19568 19930922
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Davidson, Davidson & Kappel, LLC
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 465
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of a non-steroidal anti-inflammatory drug together with an opioid analgesic in the manufacture of a medicament for the treatment of arthritis.
DETD The exclusion criteria for the study were lethargy, poor fur condition, **nasal** discharge and diarrhoea.
DETD (2) Indomethacin (Sigma), 2.5 mg/ml and 0.5 mg/ml solutions were prepared in 2% sodium bicarbonate. The **pH** was then adjusted to 7. The indomethacin was administered as a bolus orally.
IT 52-28-8, Codeine phosphate 53-86-1, Indomethacin 57-27-2, Morphine, biological studies **64-31-3**, Morphine sulfate 76-57-3, Codeine 125-28-0, DihydroCodeine 469-62-5, Dextropropoxyphene 15307-79-6, Diclofenac sodium 15307-86-5, Diclofenac 15687-27-1, Ibuprofen (pharmaceuticals contg. nonsteroidal anti-inflammatory agents and opioid analgesics)

L12 ANSWER 4 OF 10 USPATFULL
AN 1998:157363 USPATFULL
TI Peripherally active anti-hyperalgesic opiates
IN Yaksh, Tony L., San Diego, CA, United States
PA Regents of the University of California, Oakland, CA, United States (U.S. corporation)
PI US 5849761 19981215
AI US 1995-528510 19950912 (8)
DT Utility
EXNAM Primary Examiner: Spivack, Phyllis G.
LREP Seidman, Stephanie L.Heller Ehrman White & McAuliffe
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3472
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods using compositions for the treatment of peripheral hyperalgesia are provided. The compositions contain an anti-hyperalgesia effective amount of one or more compounds that directly or indirectly interact with peripheral opiate receptors, but that do not, upon topical or local administration, elicit central nervous system side effects. The anti-diarrheal compound 4-(p-chlorophenyl)-4-hydroxy-N-N-dimethyl-.alpha.,.alpha.-diphenyl-1-piperidinebutyramide hydrochloride is preferred for use in the compositions of the claimed methods.
SUMM . . . virtue of interaction with CNS opioid receptors] or CNS side-effects, including heaviness of the limbs, flush or pale complexion, clogged **nasal** and sinus passages, dizziness, depression, respiratory depression, sedation and constipation. These compounds include anti-diarrheals that act as anti-diarrheals via interaction. . .
SUMM . . . of from about 0.1%, preferably from greater than about 1%, particularly when formulated in aqueous medium for application to the **nasal** passages or lungs, up to 50% or more.
SUMM . . . applied to the eyes and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, **pH** about 5-7, with appropriate salts, and preferably containing one or more of the compounds herein at a concentration of about. . . No. 5,116,868, which describes typical compositions of ophthalmic irrigation solutions and solutions for

topical application]. Such solutions, which have a **pH** adjusted to about 7.4, contain, for example, 90-100 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium. . .

DETD . . . at 70.degree.-80.degree. C.]. Then loperamide hydrochloride in benzyl alcohol is added and finally hydroxyethyl cellulose [optional] is added and the **pH** is adjusted to 7.5 with an appropriate buffer.

DETD . . . %

(1)	
Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	5.0
Polyethylene glycol 400	5.0
White Petrolatum	10.0
Stearyl alcohol	5.0
Hydroxyethyl cellulose	--
Surfactant*	5.0
Water	qs 100
Buffer to **pH**	7.5
(2)	
Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	5.0
Polyethylene glycol 400	5.0
White Petrolatum	10.0
Stearyl alcohol	5.0
Hydroxyethyl cellulose	--
Surfactant*	5.0
Water	qs 100
Buffer to adjust **pH**	7.5

*Surfactant may be selected from, but not limited to, the following three systems: Steareth 2 plus steareth 21, or. . .

DETD

	Weight %
A.	
Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	--
Polyethylene glycol 400	--
Hydroxyethyl cellulose	1.5
Water	qs 100
Buffer to **pH**	6.5
B.	
Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	--
Polyethylene glycol 400	--
Hydroxyethyl cellulose	1.5

Water	qs 100
Buffer to **pH**	7.5

C.

Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	--
Polyethylene glycol 400	--
Hydroxyethyl cellulose	1.5
Water	qs 100
Buffer to **pH**	8.5

D.

Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	5.0
Polyethylene glycol 400	--
Hydroxyethyl cellulose	1.5
Water	qs 100
Buffer to **pH**	7.5

E.

Loperamide hydrochloride	5.0
Benzyl alcohol	2.0
Propylene glycol	5.0
Polyethylene glycol 400	5.0
Hydroxyethyl cellulose	1.5
Water	qs 100
Buffer to **pH**	7.5

DETD . . . prepared by mixing loperamide hydrochloride in benzyl alcohol and propylene glycol, adding polyethylene glycol 400 and 3350 and adjusting to **pH** 7.5 with buffer.

DETD

	Weight %

A.

Loperamide hydrochloride	5.0
Benzyl alcohol	5.0
Propylene glycol	5.0
Polyethylene glycol 3350	40.0
Polyethylene glycol 400	qs 100
Buffer to **pH**	7.5

B.

Loperamide hydrochloride	2.5
Benzyl alcohol	5.0
Propylene glycol	5.0
Polyethylene glycol 3350	40.0
Polyethylene glycol 400	qs 100
Buffer to **pH**	7.5

C.

Loperamide hydrochloride	1.0

Benzyl alcohol 5.0
Propylene glycol 5.0
Polyethylene glycol 3350
40.0
Polyethylene glycol 400
qs 100
Buffer to **pH** 7.5

IT 57-27-2, Morphine, biological studies **64-31-3**, Morphine sulfate 34552-83-5, Loperamide hydrochloride 37733-35-0 53179-11-6, Loperamide 189024-58-6
(peripherally active anti-hyperalgesic opiates)

L12 ANSWER 5 OF 10 USPATFULL
AN 1998:65234 USPATFULL
TI Pharmaceutical compositions and usages
IN Miller, Ronald Brown, Basel, Switzerland
Miller, Allan John, Surrey, England
Douglas, Stephen Gordon, Shropshire, England
PA Euro-Celtique, S.A., Luxembourg, Luxembourg (non-U.S. corporation)
PI US 5763452 19980609
AI US 1996-584658 19960111 (8)
RLI Continuation of Ser. No. US 1994-310640, filed on 22 Sep 1994, now abandoned
PRAI GB 1993-19568 19930922
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Steinberg, Raskin & Davidson, P.C.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 463
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of a non-steroidal anti-inflammatory drug together with an opioid analgesic in the manufacture of a medicament for the treatment of arthritis.
DETD The exclusion criteria for the study were lethargy, poor fur condition, **nasal** discharge and diarrhea.
DETD (2) Indomethacin (Sigma), 2.5 mg/ml and 0.5 mg/ml solutions were prepared in 2% sodium bicarbonate. The **pH** was then adjusted to 7. The indomethacin was administered as a bolus orally.
IT 52-28-8, Codeine phosphate 53-86-1, Indomethacin 57-27-2, Morphine, biological studies **64-31-3**, Morphine sulfate 76-57-3, Codeine 125-28-0, DihydroCodeine 469-62-5, Dextropropoxyphene 15307-79-6, Diclofenac sodium 15307-86-5, Diclofenac 15687-27-1, Ibuprofen
(pharmaceuticals contg. nonsteroidal anti-inflammatory agents and opioid analgesics)

L12 ANSWER 6 OF 10 USPATFULL
AN 1998:57907 USPATFULL
TI Pharmaceutical compositions for **intranasal** administration of apomorphine
IN Merkus, Franciscus W. H. M., Grootreesdijk 26, Kasterlee 2460, Belgium
PI US 5756483 19980526
WO 9422445 19941013
AI US 1995-525771 19951204 (8)
WO 1994-EP891 19940318
19951204 PCT 371 date
19951204 PCT 102(e) date
PRAI BE 1993-297 19930326
BE 1993-298 19930326
BE 1993-299 19930326
DT Utility
EXNAM Primary Examiner: Reamer, James H.
LREP Jones, Day, Reavis & Pogue

CLMN Number of Claims: 15
ECL Exemplary Claim: 1,10
DRWN No Drawings
LN.CNT 478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to pharmaceutical compositions for the **intranasal** administration of dihydroergotamine, apomorphine and morphine comprising one of these pharmacologically active ingredients in combination with a cyclodextrin and/or a disaccharide and/or a polysaccharide and/or a sugar alcohol.
TI Pharmaceutical compositions for **intranasal** administration of apomorphine
AB The invention relates to pharmaceutical compositions for the **intranasal** administration of dihydroergotamine, apomorphine and morphine comprising one of these pharmacologically active ingredients in combination with a cyclodextrin and/or a. . .
SUMM This invention is related to pharmaceutical compositions for **nasal** administration of dihydroergotamine, apomorphine and morphine, and methods of administering such compositions.
SUMM . . . for oral application, as well as for acute treatment by intravenous or intramuscular injection. DHE has been introduced in a **nasal** spray to avoid the parenteral and the oral route of administration. The **nasal** spray seems a good alternative, because it is less painful, less expensive and less inconvenient than injection therapy. Secondly, nausea and vomiting are common in migraine patients, making a **nasal** spray much more efficient than oral treatment.
SUMM A **nasal** spray containing DHE 4 mg/ml in an aqueous solution has been studied extensively by a number of investigators. Some of these investigators report, that besides DHE the **nasal** spray also contains glucose 5% and caffeine 1%. It was found that 1 mg of DHE, **nasally** administered, had the equivalence of 10 mg orally, and almost 40% of the bioavailability of the i.m. administration (PG Andersson. . .
SUMM The maximal venoconstrictor effect of 1 mg **nasal** DHE amounted to about 40%, of 0.5 mg i.m. DHE to about 50% of the initial venous diameter (W. H.. . .
SUMM **Nasal** DHE appeared to be equally effective than a combination of oral ergotamine and caffeine in relieving migraine attacks (D. Hirt et al, Cephalalgia 1989; 9, suppl. 10: 410-411). Another study in 904 patients confirmed the efficacy of **nasal** DHE and reported side effects in 18.4% of patients: **nasal** irritation, nausea, vomiting, fatigue, vertigo, breathlessness, tachycardia and perspiration. Only 3.9% of the patients refused further treatment with **nasal** DHE (G. Jenzer and M. F. Bremgartner, Schweiz. Rundsch. Med. Prax. 1990: 79: 914-917). Lataste et al (Cephalalgia 1989; 9 suppl. 10: 342-343) and Di Serio et al (Cephalalgia 1989; 9 suppl. 10: 344-345), confirm the efficacy of **nasal** DHE in the acute management of migraine. In contrast, Tulunay et al (Cephalalgia 1987; 7: 131-133) found little difference in **nasal** DHE and placebo.
SUMM Most of these studies are very encouraging and therefore **nasal** DHE, in the pharmaceutical composition studied by the above mentioned authors, seems an interesting alternative for oral and parenteral DHE preparations. **Nasal** DHE in the composition of DHE mesylate 4 mg/ml in 5% glucose and 1% caffeine, is available on prescription in. . .
SUMM Nevertheless, there is an urgent need for another DHE **nasal** drug formulation, because the **nasal** preparation, presently on the market, is not stable. It is on the market as a separate glass

ampoule (containing the DHE formulation) which has to be broken by the patient and sprayed in the **nose** using a separate spray device. After opening of the ampoule, the spray can be used no longer than 24 hours.

SUMM Accordingly, it is an object of the invention to provide a highly stable pharmaceutical composition, suitable for **nasal** administration, capable of introducing efficiently a therapeutical amount of DHE into the human body. It has surprisingly been found that a pharmaceutically acceptable DHE composition can be formulated, suitable for **nasal** administration, without the presence of a special caffeine-glucose vehicle and without the necessity of presenting the formulation in a separate. . .

SUMM According to the invention, the **nasal** pharmaceutical composition contains DHE and/or a salt of DHE (mesylate or tartrate) and a cyclodextrin and/or other saccharides and/or sugar. . .

SUMM The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

SUMM . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

SUMM **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

SUMM . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

SUMM The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of DHE in the **nasal** pharmaceutical composition of the invention, suitable in the treatment of migraine attacks, are preferably in the range from 0.25 to. . .

DETD . . . adjunctive medication in the treatment of Parkinson's disease, complicated by motor fluctuations. Recently, encouraging results have been reported on the **intranasal** application of apomorphine in patients with Parkinson's disease to relieve "off-period" symptoms in patients with response fluctuations (T. van Laar et al, Arch. Neurol. 1992; 49: 482-484). The **intranasal** applied apomorphine, used by these authors, consisted of an aqueous solution of apomorphine HCl 10 mg/ml. This formulation is also. . .

DETD The exact **nasal** composition formulation used in the study by T. van Laar et al (1992) was:

DETD . . . g

Sodium EDTA	0.010 g
NaCl	0.600 g
Benzalkonium Chloride	0.01%
NaH.sub.2 PO.sub.4.2H.sub.2 O	0.150 g
Na.sub.2 HPO.sub.4.2H.sub.2 O	0.050 g

NaOH 1 M to adjust **pH** at 5.8
purified water to 100 ml

(from Pharm. Weekblad 1991; 126: 1113-1114)

DETD . . . a metered dose nebulizer a dose of 1 mg apomorphine HCl (0.1 ml of the solution) was delivered with each **nasal** application by puff to the patients. A great disadvantage of this aqueous solution is the instability of the apomorphine.

DETD An object of the invention is a **nasal** formulation of apomorphine with an improved bioavailability and stability of apomorphine.

DETD According to the invention, the **nasal** pharmaceutical composition contains apomorphine and/or apomorphine salts and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such compositions appear to. . .

DETD The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

DETD . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

DETD **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

DETD . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

DETD The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05 ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril. Doses of apomorphine in. . .

DETD

Apomorphine HCl	500 mg
Methylated-.beta.-cyclodextrin D.S. 1.8	2.5 g
Hydroxypropylmethylcellulose	1-2 g
Benzalkonium Chloride	0.01%
Sodium EDTA	0.1%
Sodium metabisulphite	0.15%
Sorbitol	4%
pH adjusted to	4.5-5.5
purified water to	100 ml

0.2 ml gel = 1 mg Apomorphine HCl

DETD

Apomorphine HCl	1 g
Methylated-.beta.-cyclodextrin D.S. 1.1	4 g
Sodium metabisulphite	0.15%
Sodium EDTA	0.1%
Benzalkonium Chloride	0.01%
NaCl	0.8%
pH adjusted to	4.5-5.5
purified water to	100 ml

100 .mu.l = 1 mg Apomorphine HCl

DETD . . . when the parenteral route is impractical or undesirable and the

oral route is not available due to the patients condition. **Nasal** administration of a strong analgesic could be a good alternative to parenteral therapy, because it may give a very rapid. . .

DETD To overcome the drawbacks of the oral and parenteral routes of administration of morphine, the use of a **nasal** spray has been proposed (S. L. Verweij and R. van Gijn: Can morphine be administered **nasally**? Ziekenhuisfarmacie (Dutch) 1988; 4: 73-77). The composition of the **nasal** spray in this study was:

DETD

Morphine HCl.3H.sub.2 O	1.50	g
Sodium metabisulphite	0.03	g
Sodium EDTA	0.003	g
Benzylalcohol	0.3	ml
Propylene glycol	6	ml
Phosphate Buffer (0.01 mol/L; **pH** 6.00)	30	ml
Per puff of 100 .mu.1 the dose of morphine is	5	mg.

DETD . . . was delivered to the volunteers was 16 mg of morphine (range 15-18 mg) and the bioavailability of morphine from this **nasal** spray was 26-35%. The bioavailabilty of morphine after oral application is estimated to be about 40% (J. Sawe, Clin. Pharmacokinetics 1986; 11: 87-106). This means, that the bioavailability of morphine after giving the **nasal** spray as described by verweij and van Gijn is relatively low. After **nasal** absorption there is no first pass effect and therefore the **nasal** bioavailability should be higher than the oral.

DETD The **nasal** absorption of morphine has been studied also by F Chast et al (J. Pharm. Clin. 1992; 11: 257-261). They delivered **nasally** and orally 20 mg morphine acetate in an aqueous solution to 6 patients and compared the **nasal** absorption with the oral absorption of the same solution. They found, as expected, higher blood levels of morphine after the **nasal** application. Unfortunately, the **nasal** solutions, as described by the preceding studies of Verweij and van Gijn and of Chast and coworkers, are not stable. . .

DETD An object of the invention is to provide a highly stable pharmaceutical composition, suitable for **nasal** administration, and showing an superior bioavailability of morphine

DETD According to the invention, the **nasal** pharmaceutical composition contains morphine and/or morphine salts (hydrochloride, sulphate, acetate) and a cyclodextrin and/or other saccharides and/or sugar alcohols. Such. . .

DETD The **nasal** composition, according to the invention, can be administered as a **nasal** spray, **nasal** drop, suspension, gel, ointment, cream or powder. The administration of the **nasal** composition may also take place using a **nasal** tampon or **nasal** sponge, containing the invention composition.

DETD . . . advantage that no preservatives are necessary. Preservatives are known to decrease the ciliary movement, which may be harmful in chronic **nasal** medication (Hermens W. A. J. J. and Merkus F. W. H. M., Pharm. Res. 1987; 4: 445-449).

DETD **Nasal** powder compositions can be made by mixing the active agent and the excipient, both possessing the desired particle size. Other. . . less than 100 microns in diameter, preferably between 50 and 100 microns in diameter. Powders can be administered using a **nasal** insufflator. Powders may also be administered in such a manner that they are placed in a capsule. The capsule is. . .

DETD . . . literature, can be added, such as preservatives, surfactants, co-solvents, adhesives, anti-oxidants, buffers, viscosity enhancing agents, and agents to adjust the **pH** or the osmolarity.

DETD The required amount for a **nasal** administration of a liquid or semi-solid **nasal** administration form is generally between 0.05

ml and 0.2 ml, preferably about 0.1 ml per nostril. The amount of a powder **nasal** formulation is generally between 1 and 15 mg, preferably about 5 to 10 mg per nostril.

CLM What is claimed is:

1. A method of treating Parkinson's disease comprising the **intranasal** administration of a pharmaceutical powder composition containing a pharmaceutically effective amount of an ingredient selected from the group consisting of. . .

6. The method of claim 1 wherein said **intranasal** administration is accomplished by insufflation.

7. The method of claim 1 wherein said **intranasal** administration is accomplished with a jet-spray of an inert gas.

8. The method of claim 1 wherein said **intranasal** administration is in a dose of at least 0.1 mg apomorphine.

10. A pharmaceutical composition suitable for **intranasal** administration, said composition being a powder, said composition comprising a pharmaceutically effective amount of an ingredient selected from the group. . .

IT 50-70-4, D-Sorbitol, biological studies 52-26-6, Morphine hydrochloride 58-00-4, Apomorphine 63-42-3, Lactose **64-31-3**, Morphine sulfate 69-65-8, D-Mannitol 314-19-2, Apomorphine hydrochloride 511-12-6, Dihydroergotamine 596-15-6, Morphine acetate 5989-77-5, Dihydroergotamine tartrate 6190-39-2, Dihydroergotamine mesylate 7585-39-9, .beta.-Cyclodextrin 7585-39-9D, .beta.-Cyclodextrin, Me ethers 9004-54-0, Dextran, biological studies 10016-20-3, .alpha.-Cyclodextrin 17465-86-0, .gamma.-Cyclodextrin (intranasal compns. contg. therapeutic agents and cyclodextrins and saccharides)

L12 ANSWER 7 OF 10 USPATFULL

AN 97:17918 USPATFULL

TI Compositions and methods for enhanced drug delivery

IN Hale, Ron L., Woodside, CA, United States
Lu, Amy, Los Altos, CA, United States
Solas, Dennis, San Francisco, CA, United States
Selick, Harold E., Belmont, CA, United States
Oldenburg, Kevin R., Fremont, CA, United States
Zaffaroni, Alejandro C., Atherton, CA, United States

PA ~~Affymax~~ Technologies N.V., Middlesex, England (non-U.S. corporation)

PI US 5607691 19970304

AI US 1995-449188 19950524 (8)

RLI Continuation of Ser. No. US 1993-164293, filed on 9 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-77296, filed on 14 Jun 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-898219, filed on 12 Jun 1992, now abandoned And a continuation-in-part of Ser. No. US 1993-9463, filed on 27 Jan 1993, now abandoned

DT Utility

EXNAM Primary Examiner: Levy, Neil S.

LREP Stevens, Lauren L.

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 5349

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods of delivering pharmaceutical agents across membranes, including the skin layer or mucosal membranes of a patient. A pharmaceutical agent is covalently bonded to a chemical

modifier, via a physiologically cleavable bond, such that the membrane transport and delivery of the agent is enhanced.

SUMM . . . present in the solution of the pharmaceutical agent in the reservoir. Other factors that may affect the delivery rate include **pH**, concentration, extraneous ions, conductivity, and electronic factors.

DETD ii. **Nasal** Administration

DETD . . . or through the skin (i.e., transdermal), including the epidermis and dermis, or across a mucosal membrane (i.e., gastrointestinal, sublingual, buccal, **nasal**, pulmonary, vaginal, corneal, and ocular membranes), where the substance can contact, and be absorbed into, the capillaries. In certain instances,. . .

DETD . . . formed through the reaction of amines with formaldehyde and certain reactive amide compounds. N-Mannich bases have moderate stability at acidic **pH**, but rapidly hydrolyse at physiological **pH** to liberate the free amino species. N-Mannich bases possess the group --NCH.sub.2 N--.

DETD . . . linked cysteines and include 20 basic and 22 acidic residues for a net positive charge of approximately -1.69 at neutral **pH** . IFN has been used as an antiproliferative agent in the treatment of renal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma,. . .

DETD . . . comprise either permanently charged organic compounds or organic compounds which carry an ionic charge by virtue of the conditions of **pH** which exist during transmembrane or transdermal delivery. According to some embodiments, the net ionic charge of a chemical modifier (e.g., chemical modifiers comprising proteins or peptides) can be either increased or decreased by varying the conditions of **pH** during delivery.

DETD . . . pharmaceutical agent-chemical modifier complex may obtain a positive charge via protonation in the delivery buffer or formulation due to the **pH** conditions which exist during drug delivery.

DETD . . . proteins exist. The smallest histone is H4 with 103 amino acids and a net charge of approximately +18 at neutral **pH**. The largest histone H1 carries a charge of approximately +46 at neutral **pH** over approximately 207 residues. Histone H1 is rich in lysine groups. These lysine groups contain amino groups which may be. . .

DETD . . . the endocytic route offers several advantages. First, endocytotic vesicles generally fuse with acidic vesicles wherein ligand-receptor dissociation occurs at low **pH**. In addition, acid vesicles contain diverse hydrolytic enzymes including esterases and proteases. These factors can be exploited for the dissociation. . .

DETD . . . with their performance of this function. For example, platinum electrodes hydrolyze water, thus liberating hydrogen ions and subsequently, changes in **pH**. Obviously, changes in **pH** can influence the ionization state of therapeutic agents and their resulting rate of iontophoretic transport. Silver-silver chloride electrodes, on the. . .

DETD . . . are also applicable to the enhanced transport and delivery of pharmaceutical agents through mucosal membranes, such as gastrointestinal, sublingual, buccal, **nasal**, pulmonary, vaginal, corneal, and ocular membranes. See, e.g., Mackay et al. (1991) Adv. Drug Del. Rev, 7:313-338. Specifically, there are. . .

DETD ii. **Nasal**/Pulmonary Administration

DETD For delivery to the **nasal** and/or pulmonary membranes, typically an aerosol formulation will be employed. The term "aerosol" includes any gas-borne suspended phase of the pharmaceutical agent-chemical modifier complex which is capable of being inhaled into the bronchioles or **nasal** passages. Specifically, aerosol includes a gas-borne suspension of droplets of the compounds of the instant invention, as may be produced. . .

DETD . . . preferably, 1-10 mg/ml. Usually the solutions are buffered with

a physiologically compatible buffer such as phosphate or bicarbonate. The usual **pH** range is 5 to 9, preferably 6.5 to 7.8, and more preferably 7.0 to 7.6. Typically, sodium chloride is added. . .

DETD Alternatively, cleavage may be brought about by nonenzymatic processes. For example, chemical hydrolysis may be initiated by differences in **pH** experienced by the complex following delivery. In such a case, the pharmaceutical agent-chemical modifier complex may be characterized by a high degree of chemical lability at physiological **pH** of 7.4, while exhibiting higher stability at an acidic or basic **pH** in the reservoir of the delivery device. Examples of a pharmaceutical agent-chemical modifier complex which may be cleaved in such. . .

DETD . . . for 30 minutes. The reaction mixture was diluted with dichloromethane (30 ml) and washed with saturated aqueous sodium chloride. The **pH** of the aqueous layer was adjusted to 7.2 with saturated aqueous sodium bicarbonate and the aqueous layer was extracted with. . .

DETD . . . The dichloromethane solution was washed with saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride buffered to **pH** 4, and saturated aqueous sodium chloride, dried, and concentrated in vacuo to yield the desired carbonate (167 mg, 78% yield). . .

DETD . . . The reaction mixture was stirred at room temperature for 39 hours and concentrated in vacuo. The residue was triturated with **pH** 4 acetate buffer and the resulting yellow solid was filtered and dried in an vacuum oven. The yellow solid (255. . .

DETD . . . was triturated with aqueous sodium bicarbonate and extracted with chloroform 93.times.25 ml). The organic layer was washed with 50 mM **pH** 7.3 phosphate buffer, dried over sodium sulfate, and concentrated in vacuo to yield crude diester (160 mg). Column chromatography (flash. . .

IT 50-28-2, Estradiol, reactions 50-44-2, 6-Mercaptopurine 51-21-8, 5-Fluorouracil 53-86-1, Indomethacin 57-83-0, Progesterone, reactions 58-22-0, Testosterone 59-05-2, Methotrexate 60-23-1, Cysteamine **64-31-3**, Morphine sulfate 67-48-1, Choline chloride 71-63-6, Digitoxin 75-50-3, Trimethylamine, reactions 75-65-0, biological studies 79-37-8, Oxalyl chloride 100-27-6, 2-(4-Nitrophenyl)ethanol 107-15-3, 1,2-Ethanediamine, reactions 108-01-0 112-67-4, Palmitoyl chloride 141-43-5, reactions 143-62-4, Digitoxigenin 515-25-3, Betonicine 590-46-5, Betaine hydrochloride 629-11-8, 1,6-Hexanediol 761-01-3 818-08-6 818-08-6D, Di-butyl tin oxide, complex with digoxin 846-49-1, Lorazepam 924-49-2, DL-4-Amino-3-hydroxybutyric acid 927-58-2, 4-Bromobutyryl chloride 1679-53-4, 10-Hydroxydecanoic acid 2323-36-6, Deprenyl 2364-67-2 2623-87-2, 4-Bromobutanoic acid 3040-38-8 4048-33-3, 6-Aminohexanol 4224-70-8, 6-Bromohexanoic acid 4245-41-4, Estradiol-3-acetate 4521-28-2 4635-59-0, 4-Chlorobutyryl chloride 6645-46-1, L-Carnitine hydrochloride 7693-46-1, 4-Nitrophenyl chloroformate 14982-15-1 20830-75-5D, Digoxin, complexes with tin 22809-37-6, 6-Bromohexanoyl chloride 24954-67-4, 2-(4-Nitrophenyl)ethylamine 26446-35-5, Monoacetin 27532-96-3 30890-39-2 35179-98-7, Chloromethyl ethyl carbonate 36322-90-4, Piroxicam 54648-79-2 69455-04-5 75937-12-1 76812-37-8 91004-70-5 142685-32-3 144034-21-9 154270-94-7 154271-26-8 154271-59-7 154271-70-2 154294-59-4 154334-87-9
(reaction of, in prepn. of drug-chem. modifier conjugate through physiol. cleavable bond for enhanced drug transport across membranes)

L12 ANSWER 8 OF 10 USPATFULL

AN 95:75621 USPATFULL

TI Microelectrodes and their use in a cathodic electrochemical current arrangement with telemetric application
IN Broderick, Patricia A., Bronx, NY, United States
PA Research Foundation, The City University of New York, New York, NY, United States (U.S. corporation)
PI US 5443710 19950822
AI ~~US 1992~~-978449 19921118 (7)
RLI Continuation-in-part of Ser. No. US 1990-565821, filed on 14 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-395431, filed on 17 Aug 1989, now abandoned which is a continuation-in-part of Ser. No. US 1986-905579, filed on 9 Sep 1986, now patented, Pat. No. US 4883057 which is a continuation-in-part of Ser. No. US 1984-608426, filed on 9 May 1984, now abandoned
DT Utility
EXNAM Primary Examiner: Nguyen, Nam
LREP Morgan & Finnegan
CLMN Number of Claims: 32
ECL Exemplary Claim: 1
DRWN 73 Drawing Figure(s); 53 Drawing Page(s)
LN.CNT 3828
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a microelectrode comprising graphite, oil and, additionally, a compound selected from the group of lipids, glycolipids, lipoproteins, fatty acids, fatty acid derivatives, any water insoluble species and perfluorosulfonated compounds and salts thereof. This invention also relates to a method for using the microelectrode, a device that may be employed with the microelectrode, a method for making the microelectrode, and a method for using the device with the microelectrode.
DRWD FIG. 31(c) A semidifferential voltammogram showing no signal in phosphate buffer having a **pH** of 7.4 with no added chemicals. This is a stearate (1.24 cc Nujol) microelectrode.
DRWD FIG. 32 is a semidifferential voltammogram derived from the graphite stearate electrode in phosphate buffer having a **pH** of 7.4 containing 5 uM of each of DA, 5-HT, DOPAC, 5-HIAA, AA and UA on the third trial of. . .
DRWD FIG. 33 is a semidifferential voltammogram derived from the graphite stearate microelectrode (1.24 cc Nujol) in phosphate buffer having a **pH** of 7.4 containing 5 uM of each of DA, 5-HT, DOPAC, 5-HIAA, AA and UA on the fifth trial of. . .
DRWD . . . 5-HT (serotonin), DOPAC (3,4-dihydroxyphenylacetic acid), 5-HIAA (5-hydroxyindoleacetic acid), AA (ascorbic acid), UA (uric acid) and HVA (homovanillic acid), at a **pH** of 7.4 with a stearic acid electrode made from a mixture of 1.5 g carbon (graphite), 1.00 cc extra heavy. . .
DRWD . . . vitro detection of dopamine and serotonin (20 uM) in PO.sub.4 buffer containing DA, 5-HT, DOPAC, 5-HIAA, AA, UA and HVA, **pH** 7.4 with an arachidic acid electrode made from a mixture of 1.5 g carbon (graphite), 1.24 cc extra heavy Nujol. . .
DRWD . . . (semiderivative) voltammogram showing the in vitro detection of dopamine and serotonin (5 uM) in PO.sub.4 Buffer containing DA and 5-HT, **pH** 7.4 with a stearoyl cerebroside electrode made from a mixture of 0.075 g carbon (graphite), 0.05 cc extra heavy Nujol. . .
DRWD . . . detection of dopamine and serotonin (20 uM) in PO .sub.4 buffer containing DA, 5-HT, DOPAC, 5-HIAA, AA, UA and HVA, **pH** 7.4 with a stearic acid electrode made from a mixture of 1.5 g carbon (graphite), 1.00 cc extra heavy Nujol. . .
DRWD . . . vitro detection of dopamine and serotonin (20 uM) in PO.sub.4

buffer containing DA, 5-HT, DOPAC, 5-HIAA, AA, UA and HVA, **pH** 7.4 with an arachidic acid microelectrode made from a mixture of 1.5 g carbon (graphite), 1.24 cc extra heavy Nujol,. . .

DRWD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of dopamine and serotonin in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT, with a graphite microelectrode (150-200.mu. diameter; 500-750.mu. length) containing 1.5 g carbon. . .

DRWD . . . sensitivity 1 nA/V; room temperature) showing in Vitro detection of dopamine and serotonin in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT, with a graphite microelectrode (150-200.mu. diameter; 500-750.mu. length) containing 1.5 g carbon. . .

DRWD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of dopamine and serotonin in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT, with a graphite microelectrode (150-200.mu. diameter; 500-750.mu. length) containing 1.5 g carbon. . .

DRWD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of dopamine and serotonin in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT, with a graphite microelectrode (150-200 .mu. diameter; 500-750.mu. length) containing 1.5 g. . .

DETD . . . the dopamine or serotonin signal. It should be noted that oxidation potential may shift laterally, dependent on concurrent shifts in **pH**, temperature, time constants, scan rate or resistance characteristics. The detection of norephinephrine (NE) and 5-HT, using graphite stearate electrodes in. . . 15 mV less than that for NE when the electrode is not pretreated with DA, and when sensitivity, scan rate, **pH**, time constants, resistance and other relevant parameters are exactly the same. Progressive and upward amounts of NE result in an. . .

DETD . . . for dopamine and serotonin can shift to the right or the left, dependent on differences in parameters such as temperature, **pH** , various resistance and capacitance characteristics, scan increments, frequencies, scan rates and time constants and other parameters.

DETD The phosphate buffer (Na.sub.2 HPO.sub.4 : NaH.sub.2 PO.sub.4 **ph** 7.4) was made by mixing 0.02M Na.sub.2 HPO.sub.4 (dibasic) with 0.02M NaH.sub.2 PO.sub.4 (monobasic) in approximately a 4:1 ratio. Quite. . .

DETD . . . level was achieved in a period of 1.25 hours. The microelectrodes were first tested in vitro in phosphate buffer solution **pH** 7.4 (0.16M NaCl). Potentials were applied within a range of -0.001 or -0.100 to +0.5 v or higher or any. . .

DETD . . . were administered at a flow rate of six cubic feet per hour via a glove apparatus fitted over the animals' **nose** and mouth. Compressed air was administered to the animal. After a reproducible and stable baseline of extracellular dopamine and serotonin. . .

DETD . . . is measured by the semidifferential (semiderivative) voltammetry technique of Example 13, employing the phosphate buffer of Example 14, at a **pH** of 7.4, and or stearic acid-(stearate) working electrode. The stearic acid electrode is packed with 1 mg of a mixture. . .

DETD . . . (semidifferential) voltammogram showing the in vitro detection of dopamine (20 uM) and serotonin (20 uM) in phosphate buffer, at a **pH** of 7.4 with the above-described stearic acid electrode.

DETD . . . (semiderivative) voltammogram showing the in vitro detection of dopamine (20 uM) and serotonin (20 uM) in phosphate buffer at a **pH** of 7.4 with the above-described arachidic acid electrode.

DETD . . . and serotonin (5-HT) in a PO.sub.4 buffer containing the chemicals DA, 5-HT, DOPAC, 5-HIAA, AA, UA and HVA at a **pH** of 7.4. 1, 5, 10, 15 and 20 uM concentrations of each chemical were

employed in five respective tests. All. . .

DETD . . . electrode was employed for in vitro detection of dopamine (20 uM) and serotonin (20 uM) in phosphate buffer, at a **pH** of 7.4 by the steps described in Example 21. FIG. 48 shows a semiderivative (semidifferential) voltammogram of this invitro detection. . .

DETD . . . electrode was employed for in vitro detection of dopamine (20 uM) and serotonin (20 uM) in phosphate buffer, at a **pH** of 7.4 by the steps described in Example 22. FIG. 49 shows a semiderivative (semidifferential) voltammogram showing this in vitro. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate: buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. In this voltammogram, DA had no discernable peak and 5-HT had a. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

DETD . . . sensitivity 1 nA/V; room temperature) showing in vitro detection of DA and 5-HT in a 0.01M physiological saline phosphate buffer, **pH** 7.4, 10 .mu.M DA and 10 .mu.M 5-HT. The buffer was prepared according to the protocol set forth in Example. . .

IT **64-31-3**
(biogenic compds. of brain response to, detn. of, by semideriv. voltammetry in vivo)

L12 ANSWER 9 OF 10 USPATFULL
AN 84:44104 USPATFULL
TI Method of administering narcotic antagonists and analgesics and novel dosage forms containing same
IN Hussain, Anwar A., Lexington, KY, United States
PA University of Kentucky Research Foundation, Lexington, KY, United States
(U.S. corporation)
PI US 4464378 19840807
AI US 1981-258308 19810428 (6)
DT Utility
EXNAM Primary Examiner: Friedman, Stanley J.
LREP Burns, Doane, Swecker & Mathis
CLMN Number of Claims: 51
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 677
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a novel method of administering narcotic antagonists, narcotic analgesics and related compounds, and novel dosage forms containing those compounds which are adapted for **nasal** administration. The **nasal** dosage forms disclosed include solutions, suspensions, gels and ointments. Especially preferred compounds which can be advantageously administered in accordance with the invention include naloxone, naltrexone, nalbuphine, levorphanol, buprenorphine, butorphanol, .DELTA..sup.9 -tetrahydrocannabinol (THC), cannabidiol (CBD) and levonantradol.

AB . . . of administering narcotic antagonists, narcotic analgesics and related compounds, and novel dosage forms containing those compounds which are adapted for **nasal** administration. The **nasal** dosage forms disclosed include solutions, suspensions, gels and ointments. Especially preferred compounds which can be advantageously administered in accordance with. . .

SUMM . . . method of administering narcotic antagonists, narcotic analgesics and related compounds, and to novel dosage forms containing such compounds adapted for **nasal** administration.

SUMM . . . same time providing relative ease of administration when compared to intramuscular, subcutaneous or intravenous injection. This object is achieved by **nasal** administration of morphine, .DELTA..sup.9 -tetrahydrocannabinol, or one of their aforesaid phenolic, pharmacologically active analogues, advantageously formulated into a solution, suspension, ointment or gel adapted for **nasal** administration.

DRWD The FIGURE of the drawing is a semi-logarithmic plot of mean plasma levels of naloxone after intravenous, **nasal** and oral administration of a dose of 30 .mu.g of naloxone per rat.

DETD In accord with the present invention, morphine, THC and their pharmacologically active phenolic analogues can be administered **nasally** with results considerably superior to those obtained with oral administration in terms of enhanced drug bioavailability and minimization of blood. . . the disadvantages inherent in subcutaneous, intrasmuscular or intravenous administration. It would appear that these drugs are rapidly absorbed from the **nasal** mucosa into systemic blood without extensive metabolism in the gastrointestinal tract and/or extensive first-pass metabolism.

DETD . . . to examine the bioavailability of a representative drug employed in the method and compositions of the invention, namely naloxone, administered **nasally**, in comparison with the bioavailability of that drug when administered orally and intraveneously.

DETD . . . abdomen of each rat was opened through a midline incision and the drug was injected directly through the duodenum. For **nasal** administration, an incision was made in the neck of each rat and the trachea was cannulated with a polyethylene tube. Another tube was inserted from the esophagus to the posterior part of the **nasal** cavity, and the nasoplantine was closed with an adhesive agent to prevent drainage of the drug from the **nasal** cavity to the mouth. The drug was then administered to the **nasal** cavity through the tube by means of a syringe. Blood was sampled periodically from the femoral aorta. Unchanged radiolabelled naloxone. . .

DETD TABLE I below shows the individual plasma level data of naloxone from intravenous (PART A), **nasal** (PART B) and oral (PART C) routes, while the figure of drawing shows the mean plasma levels of naloxone for. . . values (AUC 0) for the individual rats for each of the three routes of administration, the bioavailability calculated for the **nasal** and oral routes, and the half-lives of elimination of the drug after intravenous and **nasal** administration.

DETD . . . 0.28

90	3.01	4.63	4.23	3.96	0.49
120	2.15	3.87	2.57	2.86	0.52
180	1.25	1.77	1.40	1.47	0.15

PLASMA LEVELS OF NALOXONE AFTER **NASAL** ADMINISTRATION OF 30 .mu.g/RAT (40 .mu.Ci/RAT) OF .sup.3 H--NALOXONE IN INDIVIDUAL RATS

1	36.20	12.71	20.97	23.29	6.88
3	41.21	30.85	42.80.	. .	

DETD . . . CURVE VALUES (AUC .sup..infin.0) FOR INDIVIDUAL RATS FROM THE THREE ROUTES OF ADMINISTRATION OF NALOXONE AND HALF-LIVES OF ELIMINATION OF NALOXONE FOLLOWING INTRAVENOUS AND **NASAL** ADMINISTRATION

I	II	III	Mean	SE	t.sub.1/2
IV	1269.7	1540.5	1685.8		
			1498.7		
				121.9	
					59.2 min.
Nasal	1904.2	1336.2	1312.0		
			1517.5		
				193.5	
					52.1 min.
Oral	19.1	11.3	35.5	22.0	7.1 --

BIOAVAILABILITY CALCULATIONS:

##STR4##

##STR5##

DETD It can be seen from TABLE II that the areas under the curve following intravenous and **nasal** administration were not significantly different, i.e. absorption of naloxone via the **nasal** route of administration was as effective as via the intravenous route. On the other hand, oral administration of 30 .mu.g. . . to only 1.5% that of the same dose given intravenously. Also from TABLE II, it can be seen that the **nasal** bioavailability of naloxone was nearly 70 times greater than the oral bioavailability.

DETD . . . also can be seen from TABLE I and the FIGURE of drawing that naloxone was very rapidly absorbed from the **nasal** mucosa; thus, at the 30 .mu.g dosage level, the peak plasma level was attained in about 5 minutes after instillation of the **nose** drops. Further, the half-life of elimination of the drug after **nasal** administration was found to be comparable to its half-life following intravenous **nasal** administration.

DETD The study described above indicates that naloxone is rapidly absorbed from the **nasal** mucosa into the systemic circulation without extensive intestinal or first pass metabolism. It is further apparent from this study that the bioavailability of naloxone when administered **nasally** is equivalent to the bioavailability of the drug when administered intravenously and vastly superior to its bioavailability by the oral. . . drug is administered orally and, consequently, for the drug's poor oral bioavailability, it follows that similar improvement in bioavailability for **nasal** versus oral administration will be observed in the case of the other phenolic drugs intended for use in the method. . .

DETD . . . for use in the present invention, i.e. morphine, THC or one of their pharmacologically active phenolic analogues, can be administered **nasally** to warm-blooded animals, conveniently by formulation into a **nasal** dosage form comprising the desired drug, in a therapeutically effective amount (i.e., depending on the selected drug, an analgesically effective. . . effective amount, an amount effective to antagonize the effects of a narcotic agent, etc.), together with a nontoxic pharmaceutically acceptable **nasal** carrier therefor. This type of composition can be used in the treatment of any of the variety of conditions which. . .

DETD . . . the case of morphine and its analogues, in the form of a pharmaceutically acceptable salt thereof. Suitable nontoxic pharmaceutically acceptable **nasal** carriers will be apparent to those skilled in the art of **nasal** pharmaceutical formulations. For those not skilled in the art, reference is made to the text entitled "REMINGTON's PHARMACEUTICAL SCIENCES", 14th edition, 1970. Obviously, the choice of suitable carriers will depend on the exact nature of the particular **nasal** dosage form desired, e.g., whether the drug is to be formulated into a **nasal** solution (for use as drops or as a spray), a **nasal** suspension, a **nasal** ointment or a **nasal** gel. Preferred **nasal** dosage forms are solutions, suspensions and gels, which contain a major amount of water (preferably purified water) in addition to the active ingredient. Minor amounts of other ingredients such as **pH** adjusters (e.g., a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the **nasal** composition is isotonic, i.e. it has the same osmotic pressure as blood serum. If desired, sustained release **nasal** compositions, e.g. sustained release gels, can be readily prepared, preferably by employing the

desired drug in one of its relatively. . .

DETD Examples of the preparation of typical **nasal** compositions containing selected drugs are set forth below. However, it is to be understood that these examples are given by. . .

DETD 1 Gram of naloxone hydrochloride is dissolved in 80 ml of distilled water and the **pH** of the resultant solution is adjusted to 7.4 with dilute sodium hydroxide solution. A quantity of water sufficient to bring. . .

DETD . . . hydrochloride, 3 grams of phenazocine hydrobromide or 5 grams of nalorphine hydrochloride in place of the naloxone hydrochloride affords a **nasal** composition containing, respectively, 5 mg of apomorphine hydrochloride, 3 mg of hydromorphone hydrochloride, 4 mg of metopon hydrochloride, 1.5 mg. . .

DETD 15 Grams of nalbuphine hydrochloride are combined with 80 ml of distilled water and the **pH** is adjusted to 4.5 with dilute sodium hydroxide solution. A quantity of water sufficient to bring the total volume to. . .

DETD . . . is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride, affording a **nasal** composition containing 15 mg of morphine sulfate per 0.1 ml.

DETD . . . the first paragraph of this example using 20 grams of pentazocine lactate in place of the nalbuphine hydrochloride affords a **nasal** composition containing 20 mg of pentazocine lactate per 0.1 ml.

DETD 1 Gram of naltrexone is dissolved in 80 ml of isotonic saline solution and the **pH** of the resultant solution is adjusted to 7.0-7.2 with dilute hydrochloric acid. A quantity of isotonic saline sufficient to bring. . .

DETD Repetition of the foregoing procedure utilizing 0.5 gram of levonantradol in place of the naltrexone affords a **nasal** composition containing 0.5 mg of levonantradol per 0.1 ml.

DETD . . . example is substantially repeated, save that 4 grams of butorphanol are employed in place of the naltrexone, to afford a **nasal** composition containing 4 mg of butorphanol per 0.1 ml.

DETD . . . the naltrexone used in the first paragraph of this example and substantial repetition of the procedure there detailed afford a **nasal** composition containing 2 mg of cyclazocine per 0.1 ml.

DETD The following are illustrative aqueous solutions of selected drugs suitable for use as **nasal** drops or **nasal** spray. In each case, the **pH** of the final composition is adjusted to 7.4. If desired, the solutions are adjusted to isotonicity.

DETD Naturally, the therapeutic dosage range for **nasal** administration of the drugs according to the present invention will vary with the size of the patient, the condition for. . . buprenorphine would be 4-8 mg per day as a maintenance dose in the treatment of narcotic addicts. The quantity of **nasal** dosage form needed to deliver the desired dose will of course depend on the concentration of drug in the composition.. . .

CLM What is claimed is:

1. A method for eliciting an analgesic or narcotic antagonist response in a warm-blooded animal, which comprises **nasally** administering to said animal: (a) to elicit an analgesic response, an analgesically effective amount of morphine, hydromorphone, metopon, oxymorphone, desomorphine,. . .

2. A method according to claim 1 for eliciting a narcotic antagonist response in a warm-blooded animal, which comprises **nasally** administering to said animal a narcotic antagonist effective amount of naxolone, naltrexone, diprenorphine, nalmexone, cyprenorphine, levallorphan, alazocine, oxilorphan, cyclorphan, nalorphine,. . .

11. A method according to claim 1 for eliciting an analgesic response in a warm-blooded animal which comprises **nasally** administering to

said animal an analgesically effective amount of nalorphine, nalbuphine, buprenorphine, butorphanol, cyclazocine, levallorphan or pentazocine, or a nontoxic. . .

15. A method according to claim 1 for eliciting an analgesic response in a warm-blooded animal, which comprises **nasally** administering to said animal an analgesically effective amount of morphine, hydromorphone, metopon, oxymorphone, desomorphine, dihydromorphine, levorphanol, phenazocine, 3-hydroxy-N-methylmorphinan, levophenacylmorphan, metazocine,. . .

30. A pharmaceutically acceptable **nasal** dosage form for eliciting an analgesic response in a warm-blooded animal, which comprises (i) an analgesically effective amount of morphine,. . . buprenorphine, butorphanol, levallorphan or pentazocine, or a nontoxic pharmaceutically acceptable acid addition salt thereof, and (ii) a nontoxic pharmaceutically acceptable **nasal** carrier therefor, said **nasal** dosage form comprising a **nasal** ointment or a **nasal** gel.

31. A dosage form according to claim 30, said dosage form comprising a **nasal** ointment.

32. A dosage form according to claim 30, said dosage form comprising a **nasal** gel.

33. A dosage form according to claim 32, said dosage form comprising a sustained release **nasal** gel.

36. A pharmaceutically acceptable **nasal** dosage form for eliciting a narcotic antagonist response in a warm-blooded animal, which comprises (i) a narcotic antagonist effective amount. . . buprenorphine, butorphanol, cyclazocine or pentazocine, or a nontoxic pharmaceutically acceptable acid addition salt thereof, and (ii) a nontoxic pharmaceutically acceptable **nasal** carrier therefor, said **nasal** dosage form comprising a **nasal** ointment or a **nasal** gel.

37. A dosage form according to claim 36, said dosage form comprising a **nasal** ointment.

38. A dosage form according to claim 36, said dosage form comprising a **nasal** gel.

39. A dosage form according to claim 38, said dosage form comprising a sustained release **nasal** gel.

42. A pharmaceutically acceptable sustained release **nasal** dosage form for **nasally** delivering systemic therapeutic levels of drug to a warm-blooded animal which comprises (i) a systemically therapeutically effective amount of a. . . nalbuphine, buprenorphine, butorphanol, pentazocine, naloxone, naltrexone, diprenorphine, nalmexone, cyprenorphine, levallorphan, alazocine, oxilorphan or cyclorphan, and (ii) a nontoxic pharmaceutically acceptable **nasal** carrier therefor.

46. A dosage form according to claim 42, said dosage form comprising a **nasal** solution, **nasal** suspension, **nasal** ointment or **nasal** gel.

48. A method for eliciting an analgesic response in a warm-blooded animal, which comprises **nasally** administering to said animal

an analgesically effective amount of a pharmaceutically acceptable **nasal** dosage form as claimed in claim 30.

49. A method for eliciting a narcotic antagonist response in a warm-blooded animal, which comprises **nasally** administering to said animal a narcotic antagonist effective amount of a pharmaceutically acceptable **nasal** dosage form as claimed in claim 36.

IT 57-29-4 62-67-9 **64-31-3** 71-68-1 71-82-9 124-92-5 127-35-5 152-02-3 314-19-2 357-07-3 357-08-4 359-83-1 1041-90-3 1239-04-9 1972-08-3 3572-80-3 13956-29-1 16590-41-3 17146-95-1 20594-83-6 23277-43-2 42408-82-2 52485-79-7 53152-21-9 58786-99-5 66429-56-9 71048-87-8 84666-77-3 84666-78-4 84666-79-5 84666-80-8 84666-81-9 84666-82-0 84697-43-8
(nasal dosage forms of, for enhanced bioavailability)

L12 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:78162 HCAPLUS
DN 98:78162
TI **Nasal** administration of narcotic antagonists and analgesics.
IN Hussain, Anwar Alwan
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8203768	A1	19821111	WO 1982-US546	19820427
	W: AU, DK, JP, NO				
	RW: AT, BE, CH, DE, FR, GB, LU, NL, SE				
	US 4464378	A	19840807	US 1981-258308	19810428
	AU 8285247	A1	19821124	AU 1982-85247	19820427
	EP 77393	A1	19830427	EP 1982-901764	19820427
	R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
	CA 1183778	A1	19850312	CA 1982-401775	19820427
PRAI	US 1981-258308	19810428			
	WO 1982-US546	19820427			

AB Narcotic antagonists, narcotic analgesics, and related compds. can be administered in **nasal** dosage forms, e.g., solns., suspensions, gels, and ointments, which provide greatly enhanced bioavailability as compared to oral, i.m., s.c., and i.v. dosage forms. Thus, 1 g naloxone-HCl [357-08-4] was dissolved in 80 mL distd. H2O and the **pH** was adjusted to 7.4 with dil. NaOH soln. H2O was added to 100 mL, and the soln. was made isotonic with NaCl soln. The soln. was sterilized by filtration through a 0.2 .mu. Millipore filter; the formulation contained 1 mg naloxone-HCl/0.1 mL. The absorption of naloxone [465-65-6] by the **nasal** route was as effective as that by the i.v. route and the **nasal** bioavailability was 70-fold the oral bioavailability in rats.

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ST narcotic antagonist analgesic **nose**

IT **Nose**
(narcotic antagonists and narcotic analgesics absorption by)
IT Narcotic antagonists
(**nasal** dosage forms of, for enhanced bioavailability)
IT Analgesics
(narcotic, **nasal** dosage forms of, for enhanced bioavailability)
IT 465-65-6
RL: PROC (Process)
(bioavailability of, from **nasal** dosage forms)
IT 57-29-4 62-67-9 **64-31-3** 71-68-1 71-82-9 124-92-5
127-35-5 152-02-3 314-19-2 357-07-3 357-08-4 359-83-1
1041-90-3 1239-04-9 1972-08-3 3572-80-3 13956-29-1 16590-41-3
17146-95-1 20594-83-6 23277-43-2 42408-82-2 52485-79-7
53152-21-9 58786-99-5 66429-56-9 71048-87-8 84666-77-3
84666-78-4 84666-79-5 84666-80-8 84666-81-9 84666-82-0
84697-43-8
RL: BIOL (Biological study)
(**nasal** dosage forms of, for enhanced bioavailability)

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Executing the logoff script...

=> LOG H

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	22.18	51.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.56	-0.56

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:46:35 ON 13 APR 2000